Original Article

Narcolepsy in Singapore: Is it an Elusive Disease?

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Abstract

Introduction: The aims of the study were to determine the demographic, clinical, and polysomnographic characteristics of narcolepsy, and to address the difficulties in diagnosing narcolepsy and cataplexy, which is a cardinal symptom. We also ventured to investigate the differences between narcolepsy with and without cataplexy. Materials and Methods: Data were collected retrospectively from patients diagnosed with narcolepsy at the Sleep Disorder Unit of Singapore General Hospital over 5 years. Each patient had had a detailed clinical evaluation and overnight polysomnography (PSG) followed by a multiple sleep latency test (MSLT). Results: A total of 28 cases were studied. Males made up 85.7% of the total and females, 14.3%. The mean age was 30.9 years. All had excessive daytime sleepiness. Other manifestations were cataplexy (48.1%), sleep paralysis (51.9%), hypnogogic hallucinations (84%), disturbed night sleep (29.2%), automatisms (17.4%) and catnaps (95.8%). The mean duration of symptoms was 7.24 years. In the MSLT, the mean values for mean sleep latency and number of sleep onset rapid eye movement (REM) periods (SOREMP) were 4.3 minutes and 2.7, respectively. Narcolepsy was associated with obstructive sleep apnoea and periodic limb movement disorder (35.7%). All the variables were compared between those who had narcolepsy with cataplexy and without cataplexy. The duration of presenting complaint, REM latency, respiratory disturbance index, number of SOREMPs and the presence of sleep paralysis were significantly different in the 2 groups. Conclusions: Narcolepsy predominantly affects young males. Concurrence of other sleep disorders is not uncommon. Some differences are evident between those who have narcolepsy with and without cataplexy.

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Key words: Cataplexy, Hypnogogic hallucinations, Rapid eye movement, Sleep paralysis

Introduction

Narcolepsy is a sleep disorder characterised by excessive sleepiness, disturbed nocturnal sleep and abnormal rapid eye movement (REM) sleep-related events, such as cataplexy, hypnogogic/hypnopompic hallucinations and sleep paralysis.[1] The population prevalence rates vary with the highest reported in Japan (0.59%)[2] and the lowest among Israeli Jews (0.00023%),[3] probably reflecting ethnic differences. There is a lack of data from Singapore. Furthermore, it remains underdiagnosed and there may be a long delay between onset and diagnosis. With this backdrop, we undertook a study to retrospectively analyse data from a group of patients with narcolepsy in order to understand the demographic, clinical and polysomnographic spectrum, as well as the problems encountered in diagnosing this disorder in the local population.

Materials and Methods

Case Ascertainment and Acquisition of Data

Data were retrospectively collected from case records of patients diagnosed with narcolepsy by a single physician (PK) at the Sleep Disorder Unit of Singapore General Hospital from January 1998 to December 2002. The sources of referral were general practitioners, primary care doctors, the emergency department and other specialists. All patients had undergone detailed clinical evaluation and overnight polysomnography (PSG) followed by multiple sleep latency test (MSLT). Case records and PSG/MSLT reports were scrutinised to obtain demographic, clinical and polysomnographic data.

Overnight PSG consisted of continuous recordings from 4 electroencephalographic (EEG) leads (C4A1, C3A2, O1A2, O2A1 of international 10 to 20 system: central

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electrodes referred to ear), 2 electro-oculographic leads, 4 electromyographic (EMG) leads (2 sub-mental and bilateral tibialis anterior), thermistors for nasal and oral air flow, strain gauges for thoracic and abdominal excursion, finger pulse oximetry and electrocardiography (ECG). The sleep stages were scored according to the international criteria of Rechtschaffen and Kales.[4] All patients maintained sleep logs, which were scrutinised prior to PSG to ensure adequate sleep hygiene. Those who were on concurrent medications for underlying medical problems were advised to discontinue sedative drugs at least a week before the test. The PSG was performed in order to diagnose other associated sleep disorders and to interpret the significance of MSLT findings.

MSLT was conducted in the morning following PSG, according to the American Sleep Disorders Association guidelines.[5] It consisted of four 20-minute nap trials at intervals of 2 hours. The recording montages were similar to that of the PSG, except that chest and abdominal strain gauges and thermistors were not included. Epochs were scored according to the rules of Rechtschaffen and Kales.[4] Two parameters were taken into consideration from MSLT; mean sleep latency and sleep onset rapid eye movement periods (SOREMPs). Sleep latency was defined as the duration in minutes from lights-out to the first epoch of sleep in each nap trial. Mean sleep latency was calculated from all 4 trials of each MSLT. SOREMPs were defined as REM sleep occurring within 15 minutes of sleep onset.

Diagnostic Criteria

The diagnostic criteria published by the American Sleep Disorders Association in the International Classification of Sleep Disorders were used.[1] The minimum criteria are excessive daytime sleepiness or recurrent daytime naps occurring almost daily for at least 3 months with a history of cataplexy. Both clinical and laboratory parameters are taken into consideration in the other set of diagnostic criteria. This combination consists of complaints of excessive sleepiness or sudden muscle weakness, associated features (sleep paralysis, hypnogogic hallucinations, automatic behaviour, disrupted major sleep episode), at least one of the polysomnographic parameters (sleep latency <10 minutes, REM latency <20 minutes, MSLT mean sleep latency <5 minutes, 2 or more SOREMPs) and the absence of any other disorder that could account for symptoms.

The main problem encountered in applying the above was confirming the diagnosis based on SOREMPs in those who had narcolepsy without cataplexy in association with other sleep disorders such as obstructive sleep apnoea (OSA) syndrome. These conditions can cause excessive daytime sleepiness as well as SOREMPs in MSLT. To overcome this difficulty, the following method was adopted. Those who had associated OSA syndrome and SOREMPs in MSLT were treated with nasal continuous positive airway pressure (CPAP) therapy first, followed by repeat PSG and MSLT while on CPAP. Those who continued to have SOREMPs despite CPAP therapy were taken into consideration for diagnosis of narcolepsy.

Statistical Analysis

Data analysis was performed using SPSS (version 10) statistical software. All demographic, clinical and polysomnographic data were analysed in the entire group of narcolepsy using descriptive statistics. Demographic variables included age, sex and ethnic distribution. The clinical characteristics analysed were presenting symptoms, duration of symptoms at presentation, clinical features and other associated sleep disorders. Polysomnographic data consisted of sleep latency, REM latency, total sleep time, sleep efficiency, percentage of delta sleep, percentage of REM sleep, arousal index, respiratory disturbance index (RDI) and periodic leg movement index (PLMI). Mean sleep latency and number of SOREMPs were analysed from MSLT.

Subsequently all patients were categorised into 2 subgroups – narcolepsy with cataplexy and narcolepsy without cataplexy. All variables between the 2 groups were subjected to univariate analysis using the Chi-square test or the Mann-Whitney U test in order to delineate the significantly different factors between the 2 groups. $P \leq 0.05$ was considered as statistically significant.

Results

A total of 28 patients were studied. Males made up 85.7% of the total and females, 14.3%. The age range was 16 to 63 years, with a mean age of 30.9 years. The ethnic composition consisted of Chinese (71.4%), Indian (14.3%), Malay (10.7%) and others (3.6%) in comparison to that of the general population (Chinese, 76.8%; Indian, 7.9%; Malay, 13.9%; and others, 1.4%).[6]

The commonest presenting symptom was excessive daytime sleepiness (EDS) (Table 1). The mean duration of symptoms was 7.24 ± 4.95 years (range, 1 to 20). Analysis of clinical data revealed that all patients suffered from EDS while a few had disturbed night sleep as well (Table 2). Concurrence of other sleep disorders was found in 35.7%. In this group, 21.5% had periodic limb movement disorder (PLMD) only, 7.1% had OSA only, and 7.1% had both OSA and PLMD. The PSG and MSLT characteristics are summarised in Table 3.

In the subgroup analysis between narcolepsy with and without cataplexy, 5 variables emerged as significantly different between the 2 groups. The narcolepsy with

Table 1. Presenting Symptoms

Symptom	%
EDS	46.3
EDS + headache	3.6
EDS + disturbed night sleep	3.6
EDS + disturbed night sleep + headache	3.6
EDS + dreams	7.2
EDS + dreams + disturbed night sleep	3.6
EDS + snoring	28.5
EDS + sleepwalking	3.6

EDS: excessive daytime sleepiness

Table 2. Clinical Features

Clinical feature	%
EDS	100
Catnaps	95.8
Hypnogogic hallucinations	84.0
Sleep paralysis	51.9
Cataplexy	48.1
Disrupted night sleep	29.2
Automatisms	17.4

EDS: excessive daytime sleepiness

Table 3. Polysomnographic Features

	Mean	Standard deviation
Sleep latency	17.8 min	35.2
REM latency	89.4 min	64.6
Total sleep time	423.8 min	72.1
Sleep efficiency	87.05%	12.3
Percentage of delta sleep	18.8%	12.1
Percentage of REM sleep	16.7%	7.6
Arousal index	12.9	9.4
Respiratory disturbance index	5.7	10.5
Periodic limb movement index	7	11.8
Mean sleep latency	4.3 min	2.7
Number of SOREMPs	2.7	0.7

REM: rapid eye movement; SOREMP: sleep onset REM period

cataplexy group demonstrated longer duration of presenting symptoms ($P = 0.046$), longer REM latency in PSG ($P = 0.024$), higher number of SOREMPs ($P = 0.044$), higher prevalence of sleep paralysis ($P = 0.021$) and lower RDI ($P = 0.043$).

Discussion

Narcolepsy is a chronic and disabling illness with considerable physical and psychosocial impact, leading to poor quality of life.[7,8] The onset usually occurs in adolescence, though cases have been reported in children and older patients.

Though this condition was first described over 100 years ago, the diagnostic criteria still remain a focus of debate. In 1957, the classic tetrad of diagnostic criteria consisting of excessive sleepiness, cataplexy, sleep paralysis and hypnogogic hallucinations was proposed.[9] Subsequently, the importance of laboratory parameters in confirming the diagnosis became apparent. The American Sleep Disorders Association formulated diagnostic criteria based on clinical features, PSG/MSLT parameters and HLA typing.[1] The recent discovery of hypocretin-1 deficiency in narcolepsy[10] has added a new marker for diagnosis. Despite this controversy, narcolepsy can still be considered a clinical diagnosis supported by laboratory parameters.

Different prevalence rates reported in different countries could be due to ethnic factors as well as methodological and diagnostic criteria differences between those studies. Among the ethnic Chinese in Hong Kong, the prevalence was found to be 0.034%.[11] The Singapore population, consisting of predominantly ethnic Chinese, is likely to closely resemble that of Hong Kong. Extrapolating the prevalence rate of narcolepsy in Hong Kong to the Singapore population of 4.16 million,[6] we would expect around 1400 patients with narcolepsy in Singapore. However, our impression is that only a fraction of this has sought medical treatment. A survey conducted in Singapore revealed only 45 cases.[12] Therefore, it is very likely that narcolepsy remains a hidden and elusive disease here.

There may be several reasons for underdiagnosis. One possible explanation is difficulty in expressing sleepiness and misinterpretation of it as a normal phenomenon. It has been shown that those with excessive sleepiness may complain of fatigue, tiredness and lack of energy rather than sleepiness.[13] Socio-cultural influences may also play a role; e.g., the disclosure of sleepiness may be considered undesirable and unacceptable. Concurrence of other sleep disorders, difficulty in recognising and delayed onset of cataplexy could make diagnosis difficult for the clinician. Above all, we believe the lack of awareness is a major cause.

It is interesting to note the concurrence of other sleep disorders. This has important diagnostic and therapeutic implications. SOREMPs in MSLT is one of the diagnostic features of narcolepsy. However, OSA can also cause SOREMPs, making interpretation of the MSLT difficult. In a previous study, we reported that 28.1% of patients with OSA have SOREMPs in MSLT.[14]

It would be useful to compare our data with studies from different populations. It has been well reported that narcolepsy is more prevalent among males.[15] However, in our sample, males comprised 85.7%, which is much higher than the figures reported in the West. This over-representation of males could perhaps be an artificial figure due to socio-cultural reasons. For example, females might not readily seek medical attention, particularly when it is difficult to express the symptoms of narcolepsy. In the

current study, patients most frequently presented in the second decade, a trend similar to findings in a study in the USA.[15]

In our study, 51.9% of patients were found to be having narcolepsy without cataplexy, as compared with 25% to 35% in larger series.[15,16] However, we observed that there was considerable difficulty in obtaining the history of cataplexy. Amongst those who had cataplexy, the history was not forthcoming in the first consultation in about 50% of patients. The history of cataplexy was elicited on repeated direct questioning in subsequent consultations. It is also possible that partial and subtle forms of cataplexy may have been missed, which could not be verified due to the retrospective nature of the study. Therefore, this high figure could be an overestimate due to smaller sample size and difficulties in eliciting the history of cataplexy. Aldrich[17] demonstrated that narcolepsy with cataplexy group had lesser slow wave sleep, more stage 1 sleep, more awakenings, lower sleep efficiency, higher incidence of sleep paralysis and sleep-related hallucinations. This contrasts with our findings where the narcolepsy with cataplexy group had a longer duration of presenting symptoms, longer REM latency (in PSG), higher number of SOREMPs, higher prevalence of sleep paralysis and lower RDI. The higher occurrence of sleep paralysis appears to be the only common finding. This association could perhaps be explained on the basis that both cataplexy and sleep paralysis are REM events. Higher number of SOREMPs in the cataplexy group is probably indicative of severity of narcolepsy in those with cataplexy. Longer duration of symptoms in the cataplexy group is understandable as cataplexy may become obvious later in the disease. We believe that our finding of longer REM latency in the cataplexy group could be due to the first night effect and has no clinical significance. However, head-to-head comparison is difficult due to the smaller sample size of our study.

Conclusion

We believe that narcolepsy is an underdiagnosed disorder in Singapore. Though the sample size is small, our study provides a useful insight into this largely underrecognised condition. It predominantly affects young adults who are in the most active stage of their lives. Symptoms may be subtle and misinterpreted as normal. Symptoms of EDS may not be obvious to the patient and it could be dismissed as tiredness, which is more culturally acceptable. Cataplexy, which is one of the cardinal features, may be absent in some. There is a need to raise awareness among the general public and the medical profession.

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